Editorials

CANCER — NATURE, NURTURE, OR BOTH

THE relative roles of genetic constitution and environmental exposure in the causation of cancer have been debated for decades.[1] Geographic differences, trends over time in the risk of cancer, and detailed studies of migrant populations overwhelmingly implicate environmental exposures as major causal factors and often identify the responsible carcinogens (e.g., tobacco, alcohol, radiation, occupational toxins, infections, diet, drugs). From this work has come the widely accepted estimate that 80 to 90 percent of human cancer is due to environmental factors.[2] Yet in the past 15 years, the explosion of molecular genetics has overshadowed environmental explanations by revealing genetic mechanisms underlying cancer. This is why the current confusion about environmental and genetic risk factors for cancer — on the part of patients, their families, clinicians, researchers, public policy makers, and the general public — is not surprising.

The gold standard for distinguishing genetic from environmental traits has been the study of twins. Comparing the incidence of disease in unrelated people, fraternal twins, and identical twins allows the heritable and environmental components of risk to be estimated. The study described by Lichtenstein and his colleagues in this issue of the *Journal*[3] has several advantages over previous studies of cancer in twins. It is population-based, the outcomes are derived from complete data on incidence, and the size of the population studied is four times as great as in any previous effort.

Although the current study has many strengths, its weaknesses illustrate the difficulties of using data on twins in studies of cancer. The study included more than 10,000 cancers in a total population of nearly 90,000 twins in Scandinavia, but the data effectively address cancer at only the four or five most common anatomical sites — and even for some of these, without much precision. The confidence intervals for the heritable proportion of susceptibility to stomach, colorectal, breast, and lung cancer all extend roughly from 5 percent to 50 percent, a fairly large range. The study lacks information on screening practices, which is quite possibly an issue in studies of twins. It also lacks data on specific types of exposure (e.g., tobacco use), so issues of interactions between genes and environment cannot be addressed. Indeed, the statistical model used specifically assumes no such interactions, ensuring that if any do exist, they will probably show up partly in the estimated environmental component of risk and partly in the heritable component. These practical limitations are inherent in studies of cancer in twins, and they indicate that delineation of the specific environmental and genetic components of the risk of cancer is likely to depend on the emerging new generation of large molecular epidemiologic studies — both population-based and family-based — rather than on studies of twins.

Despite its limitations, the study by Lichtenstein et al. provides new and valuable information for the nature-versus-nurture debate. In general, environmental factors were the dominant determinants of the site-specific risk of cancer. For cancer at four of the five common anatomical sites, estimates of the proportion of risk due to environmental effects were all 65 percent or greater. Though considerably less precise, estimates of the proportion of susceptibility that was due to environmental factors were generally even higher for cancer at the six next most frequent sites studied. These findings are consistent with the conclusions of studies of migrant groups. For example, rates of breast cancer among women who have recently immigrated to the United States from rural Asia are similar to those in their homelands and about 80 percent lower than the rates among third-generation Asian-American women, who have rates similar to or higher than those among white women in the United States.[4] This pattern is entirely consistent with the estimates by Lichtenstein et al. in this study that 73 percent of the causation of breast cancer is environmental and 27 percent heritable, particularly if a portion of the effect of heritable factors relates to genetic modification of environmental risk factors.

Although environmental effects may predominate, the findings with regard to heritability are noteworthy. Rates of concordance were generally higher in monozygotic pairs of twins than in dizygotic pairs, and the estimates of the proportion of susceptibility to cancer that was due to heritable effects ranged from 26 percent to 42 percent for cancer at the five common sites. These are substantial burdens of cancer risk, and substantially higher than estimates of risk based on a family history of a particular cancer. This degree of influence is also what would be expected if genetic effects are not limited to the rare, highly penetrant mutations that can result in familial cancer, but are also the result of polymorphisms that carry a much lower level of risk, do not result in an excess of cancer in families, and are much more prevalent than highly penetrant mutations in the general population. The most noteworthy effect of heritable factors is clearly that identified for prostate cancer (42 percent of risk). Like the other common cancers, prostate cancer shows marked international variation, and the risk among migrant groups tends to rise toward the level in the adopted country over several generations, indicating a substantial environmental component of the risk of this cancer.[5] Nonetheless,

a number of large-scale studies have searched for risk factors for prostate cancer and have found few. This lack of evidence stands in stark contrast to the situation with respect to breast, lung, and stomach cancer, for example, for which such studies have identified a variety of lifestyle-related, infectious, reproductive, and other environmental factors that are associated with moderate-to-high levels of risk. Perhaps prostate cancer does have a greater heritable component than cancer at these other sites. If some of the inherited factors are involved in modifying the risk associated with environmental factors, then success in identifying these two kinds of influences may depend on direct exploration of interactions between genes and environment.

The estimates of absolute concordance are telling. For cancer at the common sites in monozygotic twins, the rate of concordance is generally less than 15 percent. Thus, the fatalism of the general public about the inevitability of genetic effects should be easily dispelled. There is a low absolute probability that a cancer will develop in a person whose identical twin — a person with an identical genome and many similar exposures — has the same type of cancer. This should also be instructive to some scientists and others interested in individual risk assessment who believe that, with enough information, it will be possible to predict accurately who will contract a disease and who will not. With a few rare exceptions, any such deterministic approach to a disease as multifactorial as cancer seems doomed, and the data on twins seem to confirm that. This lack of absolute predictability, too, should not be surprising, given what we know about the risk of second primary cancers in paired organs.[6] For example, a woman's average annual risk of a contralateral breast cancer after the diagnosis of a first primary breast cancer is about 0.8 percent[7,8] — and this risk is for a person with, obviously, not only the identical genome, but also the identical complex of exposures.

Several things seem clear with respect to the importance of genetic and environmental factors in the causation and control of cancer. First, knowledge of one should expand our knowledge of the other. Information about types of environmental exposure that affect the risk of cancer should point to genes that might modify this risk, and the identification of genes associated with risk could help to indict previously unrecognized environmental risk factors.[9] Second, when genes and environment interact to produce a risk greater than the sum of their independent effects, this interactive component can be eliminated by removing either the genetic or the environmental factor. Finally, for cancer at many sites there are limited effective options for prevention. For this reason, unique opportunities to expand our knowledge of risk factors should be exploited regardless of their source. Perhaps it is time to drop the competition implied by talking about a debate over nature versus nurture in favor of efforts to exploit every opportunity to identify and manipulate both environmental and genetic risk factors to improve the control of cancer.

ROBERT N. HOOVER, M.D.
National Cancer Institute
Rockville, MD 20892

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BIOENGINEERED CORNEAS — THE PROMISE AND THE CHALLENGE

THE promise of bioengineered replacements for diseased or damaged tissues has become a reality, notably for skin and cartilage. The article by Tsai et al. in this issue of the *Journal*[1] demonstrates the promise of a nascent form of technology that may provide a new tool for reconstructing damaged ocular surfaces that previously would have been unrepairable.

Conditions such as the Stevens–Johnson syndrome, cicatricial pemphigoid, and chemical burns, among others, can severely compromise ocular surfaces and cause catastrophic visual loss in otherwise healthy eyes; such problems afflict thousands of patients in North America every year.[2] The global burden of blindness from these disorders is probably much greater because of the many cases of trachoma and the higher incidence of trauma outside the United States and Canada. A common pathogenic feature of this seemingly diverse group of disorders is the depletion of the stem-cell population responsible for repairing the damaged corneal epithelium.